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Symptoms and Well-Being in Relation to Glycemic Control in Type II Diabetes

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OBJECTIVE — To describe the cross-sectional relation between glycemic control and physical symptoms, emotional well-being, and general well-being in patients with type II diabetes.

RESEARCH DESIGN AND METHODS — The study population consisted of 188 patients with type II diabetes between 40 and 75 years of age. Patients were treated with blood glucose–lowering agents or had either a fasting venous plasma glucose level ≥7.8 mmol/l or an HbA_{1c} level >6.1%. Multiple regression analyses were performed. Dependent variables were scores on the Type II Diabetes Symptom Checklist, the Profile of Mood States, the Affect Balance Scale, and questions regarding general well-being. The primary determinant under study was HbA_{1c}. In addition, age, sex, neuroticism (indicating a general tendency to complain), insulin use, and comorbidity were included as determinants in all analyses. Other potential determinants taken into consideration were hypoglycemic complaints, marital status, diabetes duration, cardiovascular history, blood pressure, BMI, waist-to-hip ratio, perceived burden of treatment, and smoking. None of these potential determinants had to be included to correct confounding of the relation between HbA_{1c} and well-being scores.

RESULTS — Higher HbA_{1c} levels were significantly associated with higher symptom scores (total score, hyperglycemic score, and neuropathic score), with worse mood (total score, displeasure score, depression, tension, fatigue), and with worse general well-being. The relative risks varied between 1.02 and 1.36 for each percentage difference in HbA_{1c}. The relation between HbA_{1c} and some mood states was modified by neuroticism: in the less neurotic patient (i.e., one who is less inclined to complain), the relation was more evident.

CONCLUSIONS — These data suggest that better glycemic control in type II diabetes is associated with fewer physical symptoms, better mood, and better well-being, in a nonhypoglycemic HbA_{1c} range.

In type II diabetes, optimization of metabolic control may be seen as a tool to reduce the risks of long-term hyperglycemic complications. In addition, clinical experience suggests that in the short term, improvement of glycemic control can reduce feelings of anxiety or fatigue (1). Many diabetologists will confirm, if only from experience or from published case series, that in type II diabetes, a change from maximum dosage of tablets to insulin therapy often leads to marked improvements in well-being (2–4). This improvement may be attributed to the accompanying education and treatment satisfaction: the majority of patients find insulin therapy easier than expected (5,6). However, the reduction of any degree of hyperglycemia itself may also influence well-being through minimizing symptoms associated with hyperglycemia.

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ABS, affect balance scale; DSC-Type 2, Type II Diabetes Symptom Checklist; OR, odds ratio; POMS, Profile of Mood States; RGM, ratio of geometric means; VA CSDM, Veterans Affairs Cooperative Study of Diabetes Mellitus.

Although the severity of classic hyperglycemic symptoms (thirst, polyuria, and weight loss) broadly parallels the degree of hyperglycemia (7), this relation is alleged to be present only when glucose levels exceed the renal threshold (8). Aside from the classic triad, hyperglycemia can also be accompanied by nonspecific symptoms such as pruritus, fatigue, drowsiness, or feelings of depression (3); asymptomatic hyperglycemia is, in fact, rather uncommon (9). However, even the classic symptoms are not always recognized (9), and feelings such as drowsiness and depression are not generally ascribed to hyperglycemia (3). For patients in whom no concrete symptoms seem to be present beforehand, improvement in well-being upon lowering of glycemic level could be attributable to diminution of less tangible signs, such as tension, lethargy, and difficulty in concentrating. If this were true, a relation between well-being and glycemia might even be present at levels closer to normoglycemia, which would be extremely relevant to the discussion of target values for glycemic control in type II diabetes.

Many of the nonspecific symptoms can be viewed as an expression of a depressed mood, which could be influenced by the degree of hyperglycemia, with or without physical complaints intermediating. However, negative feelings are also associated with problems in coping with chronic illness in general (10, 11). The objective of this study was to establish the cross-sectional relation between glycemic control and measures of well-being in patients with type II diabetes. We expected this relation—if at all present—to be such that higher glycemic levels would be accompanied by worse well-being. Subjective well-being was assessed using complementary approaches: *1*) the assessment of physical symptoms related to diabetes; 2) assessment of emotional well-being (mood); and 3) overall evaluations of general well-being. Personality, medical history, insulin treatment, and marital status were among the variables taken into consideration as potential confounders.

RESEARCH DESIGN AND METHODS

Study population

Twenty-seven of 31 general practitioners in Hoorn (The Netherlands) agreed to take part in this study. Participating general practitioners made lists of all of their patients with known type II diabetes. From this list, only those patients who were white, between 40 and 75 years of age, and who were not considered (by their own physicians) too immobile to visit the study center were invited to participate in our study. Of all positive responders (221 patients, 71% of those invited), 27 patients were not treated with blood-glucose–lowering agents and had both a fasting venous plasma glucose level <7.8 mmol/l and an HbA_{1c} level ≤6.1%, suggesting (near) normal glucose tolerance. Data were insufficient for six patients. The remaining 188 patients were included in this analysis.

Measurements

Potential determinants. HbA_{1c} levels were determined by ion-exchange high-performance liquid chromatography, using the Modular Diabetes Monitoring System (Bio-Rad, Veenendaal NL, The Netherlands; normal range, 4.3–6.1%). BMI was calculated as weight (kilograms) divided by height squared (square meters). The waist-to-hip ratio was computed as waist circumference divided by hip circumference. Systolic and diastolic (Korotkoff V) blood pressures were measured on the right arm of the seated patient with a Hawksley random zero sphygmomanometer, after a rest of at least 10 min.

A history of cardiovascular events was considered to be present if a myocardial infarction or a stroke had taken place at any time in the past, if angina pectoris had been confirmed by a cardiologist, if a transient ischemic attack had been diagnosed by a general practitioner or a neurologist, or if typical intermittent claudication, according to a standard questionnaire, was present. Patients were asked to bring the drugs that they took with them to the study center. The use of bronchodilators was assumed to indicate the presence of chronic obstructive pulmonary disease. All patients were asked whether they had any other disease or complaint other than diabetes. Chronic pain due to arthritis or arthrosis and chronic back pain were recorded as complaints of the locomotor system.

Referring to the previous 3 months, patients were asked if they had experienced any episodes of sweating, weakness, hunger, dizziness, etc. If these symptoms had disappeared shortly after taking carbohydrate in any form, they were assumed to indicate hypoglycemia. Hypoglycemia was recorded if the episodes did not occur just before a planned meal or in connection with unusual physical exertion (grade 2), and if help from others had been necessary to regain normoglycemia (grade 3).

Patients were asked to indicate the perceived burden of their diabetes treatment on a four-point Likert scale. All patients completed the Netherlands Personality Questionnaire (12). Of special interest to the objective of this study is the dimension of neuroticism, which consists of 21 items reflecting tendencies toward vague fears, vague physical signs, depressed mood, and feelings of insufficiency. People with high scores on this dimension are known to report more symptoms and can be described as generally emotional, tense, insecure, or gloomy (range: 0, least neurotic; 42, most neurotic). This questionnaire has been validated in various populations, whereby the neuroticism subscale exhibited a median internal consistency coefficient (α) of 0.86 and a test-retest reliability between 0.77 and 0.86 (12).

Outcome measures. We used the Type II Diabetes Symptom Checklist (DSC-Type 2) (13) to measure the frequency and perceived burden of diabetes-related symptoms. The DSC-Type 2 consists of 34 items in six dimensions: hyperglycemic, hypoglycemic, neuropathic (subdivided into pain symptoms and sensory symptoms), psychological (subdivided into fatigue and cognitive distress), cardiovascular, and ophthalmological. Each item is scored on a frequency scale and, if a symptom is present, also on a discomfort scale. Multiplication of each frequency with its corresponding discomfort score yields weighted scores per item. From these, a weighted score for each (sub)dimension can be calculated. The DSC-Type 2 explicitly refers to the month preceding the visit. For the total symptom score, all subscales are added. Because the original hyperglycemic dimension consists only of items reflecting polyuria and polydipsia, we have renamed it "classic hyperglycemic." A new hyperglycemic score was computed by combining weighted scores of classic hyperglycemic, fatigue, and cognitive distress because, in our view, these dimensions are most directly related to the present glycemic status (as opposed to a longer-term history of hyperglycemia).

The Dutch shortened Profile of Mood States (POMS) (14) was used to measure current emotional well-being. The POMS (32 items) consists of four negative dimensions (depression, anger, fatigue, and tension) and one positive dimension (vigor), explicitly referring to "the past few days, including today" only (15). From its dimensions, an aggregate mood score can be calculated. To obtain a more pure measure of mood state that would be less influenced by physical fatigue, we computed a displeasure score as the sum of the depression, anger, and tension dimension scores.

As a more general measure of well-being, the Affect Balance Scale (ABS) was used (16). The ABS consists of five positive and five negative items, adding up to a positive, a negative, and an aggregate balance score. In our study, the ABS explicitly referred to the previous 3 weeks. All (sub)scores on DSC-Type 2, POMS, and ABS were transformed to a 0–10 scale, in which lower scores indicate higher levels of well-being.

Referring to the previous 3 months, subjects were asked to score their perceived health ("How would you describe your current state of health?") and to give two overall evaluations of their quality of life ("How did you feel, all things considered. . ."; "How satisfied were you, all things considered, with your life. . .") on five-point Likert scales. All questionnaires were introduced to the patients by the investigator and completed by the patients at the study center. All measurements were performed during a visit to the study center, except for the personality questionnaire, which was postponed until 6 months later, because *1*) we anticipated interference between questionnaires, 2) we wanted to avoid an overload of questionnaires at the visits, and 3) personality traits can be considered constant over shorter periods of time.

Statistical analysis

Spearman rank-correlation coefficients were calculated to detect any univariate

relation between the (often skewed) outcome measures and all potential determinants. Univariate relations between HbA_{1c} and all other variables considered were studied by cross-tabulations and scatterplots. Outcome measures were selected for further multiple regression analysis if the correlation coefficient with HbA_{1c} was >0.15. After logarithmic transformation, some outcome measures, based on a sufficiently large number of items, could be analyzed by ordinary regression analysis, as judged from the normal distribution of the residuals. The other outcome measures were dichotomized at their median value and analyzed by means of logistic regression analysis.

Determinants were included in the following order. First, some variables that are generally believed to be associated with symptoms and well-being and, in our study, showed a statistically significant rank correlation with at least two of the outcome measures selected for multiple regression analysis were included. Thus, age, sex, insulin therapy (yes or no), and complaints of the locomotor system (yes or no) were included in model 1. Next, neuroticism was added (model 2), followed by HbA_{1c} (model 3). Squared determinants and product terms of HbA_{1c} (with the determinants included) were added if they were statistically significant (with a preference for product terms if a choice was necessary). Finally, all other determinants were included one by one, to check whether inclusion would influence the magnitude or precision of the HbA_{1c} regression coefficient.

In the case of logistic regression analysis, the role of HbA_{1c} in determining subdimensions of well-being was expressed as the odds ratio (OR) per unit difference in HbA_{1c}. In logistic regression analysis, calculating the antilog of the regression coefficient b of a determinant (e^b) directly results in the OR per unit difference in that determinant, adjusted for all the other determinants in the model. In the regression equations with log-transformed outcome measures, the antilog of the HbA_{1c} regression coefficient (10^b) can be interpreted in a way similar to the OR: it is the ratio of geometric means (RGM) corresponding to one unit (percentage) difference in HbA_{1c}. For example, if the RGM of a determinant equals 1.05, the (geometric) mean level of the outcome increases by 5% for each unit increase in the determinant (a geometric mean is obtained when the mean of a log-transformed variable is backtransformed by calculating the antilog) (17). The standard error of the regression coefficient was used to obtain the 95% CI of the RGMs and the ORs. All reported P values are two-tailed.

Table 1—*Characteristics of study population by sex*

	Men	Women
n (% of total)	85 (45.2)	103 (54.8)
Age (years)	62.2 ± 8.9	64.4 ± 7.9
Marital status		
Married/living together	68 (80.0)	64 (62.1)
Single	8 (9.4)	7 (6.9)
Widowed	5 (5.9)	24 (23.5)
Separated/divorced	4 (4.7)	8 (7.8)
Duration of diabetes (years)	3.7 (1.9–9.3)	4.3 (1.8–8.2)
Diabetes therapy		
Diet only	20 (23.5)	22 (21.4)
Sulfonylurea and/or metformin	51 (60.0)	61 (59.2)
Insulin	14 (16.5)	20 (19.4)
Glycemic control		
HbA_{1c} (%)	7.2 ± 1.5	7.7 ± 1.9
Fasting plasma glucose of patients on diet and/or tablet treatment (mmol/l)	9.4 ± 2.5	9.8 ± 3.5
History of cardiovascular events	25 (29.4)	19 (18.4)
Myocardial infarction	14 (16.5)	9 (8.7)
Angina pectoris	9 (10.6)	9 (8.7)
Transient ischemic attack or stroke	7 (8.2)	7 (6.8)
Intermittent claudication	4 (4.7)	3 (2.9)
Urinary albumin/creatinine ratio		
>3.5	19 (22.4)	16 (15.5)
>35.0	4 (4.7)	5 (4.9)
Systolic/diastolic blood pressure (mmHg)	147 ± 21/84 ± 11	154 ± 22/84 ± 11
Blood pressure–lowering medication (all indications)	29 (34.1)	47 (45.6)
BMI (kg/m^2)	27.9 ± 3.2	29.4 ± 5.5
Waist-to-hip ratio	0.99 ± 0.06	0.91 ± 0.07
Current smokers	20 (23.5)	18 (17.5)
Chronic locomotor complaints	6 (7.1)	8 (7.8)
Medication for chronic obstructive pulmonary disease	10 (11.8)	4 (3.9)
Neuroticism scale (0–42)	8 (4–15)	14 (8–21)

Data are means ± SD, *n* (%), or median (interquartile range).

RESULTS — In Table 1, the characteristics of the study population are summarized for men and women separately. Glycemic control exhibits a wider range and is slightly less satisfactory in women than in men ($P = 0.05$). In accordance with earlier studies, women show higher scores than men on the neuroticism scale of the personality questionnaire ($P < 0.0001$); median scores for both sexes are comparable to scores for the reference groups (12). As was expected because of overlapping domains, we found the different measures of well-being to intercorrelate to a limited extent (r between 0.25 and 0.55, data not shown).

Table 2 presents the distributions of the outcome measures in tertiles of HbA_{1c}. It is clear from the low median and 75th percentile values that the distribution of all measures, except the aggregate DSC-Type 2 and POMS scores, is highly skewed. All dimension and aggregate DSC-Type 2 and POMS scores, except hypoglycemic, cardiovascular, ophthalmological, and vigor, show a clear trend suggesting a lower degree of well-being with higher HbA_{1c} values, which is confirmed by the statistically significant Spearman

Table 2—*Measures of well-being: distributions of scores by tertiles of HbA_{1c} and rank correlations with HbA_{1c}*

HbA_{1c} category	Median (75th percentile) Low	Medium	High	Correlation with HbA_{1c}
DSC-Type 2				
Fatigue	0.8; 1.7	0.8; 2.1	1.0; 3.1	0.14*
Cognitive distress	0.0; 1.1	0.4; 1.7	0.6; 2.5	0.16*
Sum: psychological	0.5; 1.6	0.8; 1.7	0.9; 2.3	0.16*
Classic hyperglycemic	0.4; 1.7	0.4; 2.1	0.8; 3.8	0.16*
Sum: hyperglycemic	0.5; 1.8	0.9; 1.8	1.3; 2.7	0.19†
Hypoglycemic	0.0; 1.1	0.0; 0.6	0.0; 0.6	−0.02
Sensory neuropathic	0.0; 0.8	0.3; 1.4	0.3; 1.1	0.16*
Pain neuropathic	0.0; 0.0	0.0; 0.4	0.0; 1.3	0.14
Sum: Neuropathic	0.0; 0.7	0.3; 1.0	0.3; 1.6	0.15*
Cardiovascular	0.0; 0.8	0.4; 0.8	0.4; 1.7	0.11
Ophthalmological	0.0; 1.0	0.0; 1.0	0.2; 1.3	0.04
Sum: total	0.4; 1.0	0.6; 1.2	0.9; 1.9	0.23‡
POMS				
Depression	0.0; 0.3	0.0; 1.3	0.3; 0.9	0.16*
Anger	0.4; 1.1	0.4; 1.4	0.7; 2.5	0.19†
Tension	0.8; 1.7	1.3; 2.9	2.1; 2.9	0.20†
Sum: displeasure	0.4; 1.2	0.8; 1.5	1.0; 1.8	0.22†
Fatigue	0.4; 1.4	0.8; 1.3	1.3; 2.5	0.29‡
Vigor	3.5; 5.0	3.0; 5.0	3.5; 6.5	0.07
Sum: total	1.2; 1.9	1.5; 2.5	1.9; 3.0	0.23†
ABS				
Negative	0; 2	2; 4	2; 4	−0.10
Positive	2; 4	2; 4	2; 4	−0.00
Aggregate: balance	2; 3	2; 3	2; 3.5	−0.06

Scales of all outcome measures (given on the left side) are 0.0–10.0 (best well-being–worst well-being). Categories of HbA_{1c} are tertiles; HbA_{1c} per tertile [median (range)]; low 6.0 (4.0–6.4)%; medium 7.2 (6.5–7.9)%; high 8.8 (8.0–15.3)%. *$P < 0.05$. †$P < 0.01$. ‡$P < 0.001$.

rank-correlation coefficients. Scores on the ABS were not significantly correlated to HbA_{1c}. Of the three overall evaluations of well-being, the general sense of well-being and the perceived health status were significantly correlated with HbA_{1c} (0.22, $P < 0.01$ and 0.31, $P < 0.001$, respectively), again suggesting better well-being and perceived health with lower HbA_{1c}.

Table 3 summarizes the results of the linear regression analyses with four log-transformed outcome measures, in terms of proportion of total variation explained by the models (R^2). Clearly, neuroticism explains a considerable part of the variation of both the DSC-Type 2 and the POMS scores. The contribution of HbA_{1c} to the proportion of variation explained by regression (average, 0.02 or 2%), although small, is statistically significant for all four outcome measures.

In Table 4, the RGMs and ORs of HbA_{1c} are given for the DSC-Type 2. For example, the (geometric) mean hyperglycemic score is 1.05 times higher with an HbA_{1c} of 7.0% than with an HbA_{1c} of 6.0%; for an HbA_{1c} difference of 2%, the mean hyperglycemic score has to be multiplied by $(1.05)^2 = 1.10$. In the logistic regression analyses, the ORs of HbA_{1c} were statistically significant for the classic hyperglycemic and the neuropathic dimension of the DSC-Type 2.

Table 4—*Multiple regression analyses for strength of the relation between HbA_{1c} and scores on the DSC-Type 2*

	% HbA_{1c}
RGM: linear regression	
Hyperglycemic score	1.05 (1.01–1.10)
Total score	1.03 (1.00–1.07)
OR: logistic regression	
Cognitive	1.13 (0.92–1.40)
Psychological sum score	1.11 (0.91–1.35)
Classic hyperglycemic	1.22 (1.01–1.47)
Sensory neuropathic	1.14 (0.95–1.37)
Total neuropathic	Product term

Data are point estimates (95% CI). Outcome measures are given on the left side. Only hyperglycemic score and total score could be analyzed by linear regression, as judged from the distribution of the residuals. All models include HbA_{1c}, neuroticism, age, sex, insulin use (yes or no), and self-reported chronic complaints of the locomotor system (yes or no). In the model for total neuropathic symptoms, the product term ($HbA_{1c} \times$ neuroticism) was also significantly included ($P = 0.02$), indicating that the influence of HbA_{1c} on neuropathic complaints varies according to level of neuroticism. OR of HbA_{1c} at the 25th and 75th percentiles of neuroticism: 1.39–1.02.

For the POMS dimensions of depression, tension, and fatigue, a higher HbA_{1c} level was significantly associated with higher scores (Table 5). There were clear indications that the strength of the relation between HbA_{1c} and several POMS scores depended on the level of neuroticism. To illustrate what this so-

Table 3—*Linear regression analyses with well-being sum scores, log-transformed, as outcome measures; influence of consecutively adding neuroticism and HbA_{1c} to a basic set of determinants (model 1) on the proportion of variation explained by regression*

	R^2 model 1	R^2 model 2: neuroticism included	R^2 model 3: neuroticism and HbA_{1c} included
DSC-Type 2			
Hyperglycemic score	0.180	0.318	0.338
Total score	0.155	0.270	0.285
POMS			
Displeasure score	0.126	0.322	0.353
Total score	0.150	0.348	0.362

Only the four outcome measures on the left side could be analyzed by linear regression, as judged from the distribution of the residuals. Model 1 includes the following determinants: age, sex, insulin use (yes or no), and self-reported chronic complaints of the locomotor system (yes or no). Whenever statistically significant, the product term ($HbA_{1c} \times$ neuroticism) was included as well.

Table 5—*Multiple regression analyses for strength of the relation between HbA_{1c} and scores on the POMS, with and without taking into account interaction between HbA_{1c} and neuroticism, adjusted for other determinants*

	% HbA_{1c}			
		With interaction		
	Without interaction	25th percentile of neuroticism	75th percentile of neuroticism	*P* value product term
RGM: linear regression				
Displeasure score	1.02 (0.99–1.06)	1.07	1.01	0.04
Total score	1.03 (1.00–1.06)	—	—	0.10
OR: logistic regression				
Depression	1.09 (0.90–1.33)	1.37	1.02	0.06
Anger	1.03 (0.86–1.23)	—	—	0.29
Tension	1.39 (1.09–1.78)	1.87	1.15	0.01
Fatigue	1.36 (1.10–1.69)	—	—	0.21

Data are point estimates (95% CI). Outcome measures are given on the left side. Only displeasure score and total score could be analyzed by linear regression, as judged from the distribution of the residuals. The reported ORs and RGMs are adjusted for neuroticism, age, sex, insulin use (yes or no), and self-reported chronic complaints of the locomotor system (yes or no). For the with-interaction data, if the product term (HbA_{1c} × neuroticism) is significantly included (interaction), the influence of HbA_{1c} on the outcome measure varies according to level of neuroticism. Therefore, the ORs and RGMs corresponding to two different levels of neuroticism are given.

called interaction or effect modification implies, the RGMs and ORs of HbA_{1c} for less neurotic people and for people on the more neurotic side (the 25th and 75th percentiles of neuroticism, respectively) are listed in Table 5. As an example, in people normally not inclined to complain about physical signs and worse mood (i.e., at the 25th percentile of neuroticism), the mean displeasure is 1.18 times less favorable with an HbA_{1c} of 8.0% than the mean displeasure accompanying an HbA_{1c} of 5.5% ($1.07^{2.5}$). In people characterized by a tendency to complain (i.e., at the 75th percentile of neuroticism), the same HbA_{1c} difference is associated with an RGM for displeasure equal to $1.01^{2.5}$ = 1.03. The strongest relation with HbA_{1c} was found in POMS tension (nervous, panicky, tense, restless, anxious, or insecure): at the 25th percentile of neuroticism, the OR of 1% HbA_{1c} difference was 1.87.

The displeasure score contains no items that could readily be interpreted as physical. Therefore, it offers the opportunity to investigate whether the relation between HbA_{1c} and (pure) mood state was mediated by physical symptoms. To this end, a regression analysis was performed with displeasure as the outcome measure and with the total DSC-Type 2 score added as a determinant to model 3. In this analysis, the proportion of variation explained rose to 0.458, whereas the magnitude of the HbA_{1c} regression coefficient did not differ substantially from that in model 3 (data not shown).

Logistic regression analyses using the two general well-being items significantly correlated with HbA_{1c} as outcome measures, with the determinants of model 3, again indicated that with higher HbA_{1c} levels, the probability of finding less favorable well-being scores rises. A 1% HbA_{1c} difference was associated with ORs of 1.30 (95% CI: 1.07–1.58) and 1.21 (95% CI: 1.01–1.47) for general well-being and perceived health, respectively. Both items were dichotomized between the two most prevalent answering categories of the five-point Likert scales (0 = good or better; 1 = not good, not bad or worse).

If rather than HbA_{1c} values, fasting glucose levels were included in the analyses presented in Tables 2 through 5, all effects pointed in the same direction but had larger *P* values (data not shown). Of all the determinants not included in the regression models, none appeared to be a confounder of the relations found, nor did we find any variables consistently making a statistically significant contribution when added to model 3. Particularly worth mentioning here are marital status, hypoglycemic episodes (>grade 1) in the previous 3 months, history of cardiovascular events, and perceived burden of treatment, because we expected these variables to predict, to some extent, the scores on our outcome measures. However, not many participants experienced more than a little burden of their diabetes treatment (8.1%), and hypoglycemic complaints were not very common and were seldom verified by self-monitoring of blood glucose. The few people who reported experiencing one or more hypoglycemic episodes during the 3 months preceding the measurements (n = 15, 8.0%) had higher hypoglycemic scores on the DSC-Type 2 (P = 0.006) and a slightly lower HbA_{1c} level (0.8%, P = 0.04) compared with the rest of the study population. Nevertheless, no direct relation was found between HbA_{1c} and the hypoglycemic dimension (Table 2). Recent (adverse) life events, possibly negatively influencing well-being scores, were recorded if they were mentioned by the patients. Excluding these cases (n = 8) from the analysis did not change the results.

CONCLUSIONS — It will be clear that well-being can seriously be diminished by the development of diabetic complications and by frequent hypoglycemia (1,18). In patients with type II diabetes, definite conclusions about the role of long-term glycemic control in preventing complications cannot be drawn yet but may eventually arise from a goal-directed trial of the Veterans Affairs Cooperative Study of Diabetes Mellitus (VA CSDM) group (19) and possibly from the U.K. Prospective Diabetes Study (20). The objective of the present study was to assess whether a cross-sectional relation could be found between glycemic control and well-being, which could indicate a more direct, short-term influence of hyperglycemia on the well-being of patients with type II diabetes.

We found a statistically significant relation between glycemic level and several symptom and mood scores. The associations were not very strong: the glycemic level only explained a small part of the variation in well-being. However, the direction of the relations was as expected: higher glycemic levels were associated with worse well-being scores. The finding that people with higher glycemic levels report being in a worse mood holds true, even when the results were adjusted for total level of physical symptoms. Al-

though the DSC-Type 2 may not cover all diabetes-related complaints, this finding suggests that the relation between glycemic level and mood is probably not entirely mediated by the presence of physical symptoms. The lack of association between HbA_{1c} and the hypoglycemic subscore could be due to the content of the items in this dimension: all three items address the moodiness that is sometimes reported during hypoglycemia, rather than the physical signs of hypoglycemia (13).

If we had not measured neuroticism, this would not have made much difference to our conclusions regarding physical symptoms: apart from the dimension of total neuropathy, none of the relations was modified by neuroticism. In contrast, it would have made a substantial difference in our study of emotional well-being: without the possibility of taking into account degree of neuroticism, fewer dimensions would have been significantly related to the outcome measures, indicating an important gain in the precision with which the relation could be described. The reason for this difference between both outcome measures is most likely to be found in the nature of the items in the questionnaires: physical symptoms are probably less sensitive to individual perception than feelings.

The importance of selecting the appropriate instrument for assessing well-being may be illustrated by the outcome of the ABS measures. In this study, a so-called generic instrument such as the ABS was not able to detect differences associated with disease-specific biological parameters such as glycemic level. The VA CSDM group have reported that, contrary to what could be expected, a considerable difference in glycemic control (an HbA_{1c} difference of 2% between the treatment groups) is not accompanied by a difference in well-being (21). The choice of instrument may have played a role in this and another negative study outcome (21,22).

Our cross-sectional finding of an interaction between HbA_{1c} and neuroticism suggests that any benefit of improving unsatisfactory glycemic control in terms of both diabetes-related symptoms and emotional well-being would probably be most clearly noticeable in patients who are known by their physician normally not to complain very often (without reason). In patients with a less favorable psychological makeup, the effects of diminishing hyperglycemia might also lead to a decrease in the symptom burden, but the effect on emotional well-being could be masked by their general gloominess and tendency toward adverse feelings.

We cannot conclude from our study that a change in glycemic levels over time will cause a concurrent change in well-being. Such a definite conclusion would have to be supported by experimental data. However, even without an experimental contrast, a study relating repeated measurements of well-being to repeated measurements of glycemic control could be more convincing than the present design. An example of this approach in type I diabetes is provided in the study by Mazze et al. (23), which although designed as a randomized clinical trial, was analyzed as a nonexperimental cohort study because a clear experimental contrast could not be established. The fact that, despite the longitudinal character of their study, Mazze et al. were left in doubt about the direction of causality of the relation observed is illustrative of the intricacy of the subject matter under study here. In patients with diabetes, there are treatment-related factors involving, for instance, lifestyle changes as well as different modalities of therapy; there are patient-related factors such as personality and social background; and there are prior conditions involving, for instance, the care system and the attitudes of several caregivers. All of these interrelated and often overlapping factors lead to a process that results in objective outcomes, such as the degree of hyperglycemia, and subjective outcomes, such as physical complaints, mood, and general feelings of well-being. These outcomes are potentially determined by all factors and conditions in the process.

To obtain certainty about the role of glycemic control in subjective well-being, we need appropriately controlled experimental data (ideally, comparison of two different glycemic levels while all other conditions are equal). For the time being, we can only conclude that our cross-sectional results are consistent with the view that better glycemic control enhances well-being.

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